Templating Photodimerization of Coumarins within a Water-Soluble Nano Reaction Vessel

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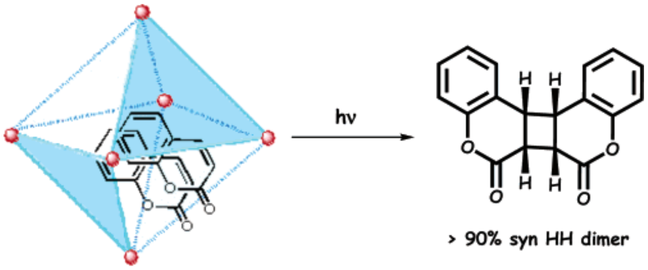

An octahedral Pd nanocage serves as a reaction vessel to control photodimerization of coumarins in water. The coumarin derivatives explored in this study react within the Pd nanocage to selectively yield a syn head−head dimer, whereas in water, they yield either a mixture of dimers or a different isomer. The selective dimerization is interpreted to mean that the monomers are preorganized by the cage through weak intermolecular forces. The selectivity obtained within the nanocage is more general and predictable compared to other hosts used previously to control the geometry of photodimerization reactions.

Introduction

During the last two decades, there has been continued interest in controlling excited-state processes through the use of confined and well-ordered media. The media included crystals, solid host−guest complexes, water-soluble host−guest complexes, liquid crystals, polymers, micelles, zeolites, clays, and silica.[1] The extent of selectivities with these media varied, and the search for an ideal and more versatile confined medium still continues. In this report, we present our results on the use of a water-soluble nano reaction vessel in controlling photodimerization reactions. The nano reaction vessel that we explored is the commercially available Pd nanocage originally synthesized and explored by Fujita and co-workers.[2] The photoreaction we investigated is the dimerization of coumarins.[3] Our ability to steer the photoreactions of four coumarin derivatives into a single dimer (syn head−head) illustrated the extent of control one could achieve within the above nano reaction vessel in aqueous medium.

Our interest in controlling photodimerizations of olefins dates back to the 1980s when we carried out the dimerization of coumarins, stilbenes, and cinnamic acids in aqueous and micellar media.[4] While we succeeded in enhancing the reactivity, controlling the regiochemistry of addition in these media was elusive. It is in this context that we explored the use of the Pd nanocage as a reaction vessel. We chose four coumarins (**1a**−**1d**) (Scheme 1) as models.[3] The choice was dictated by the fact that these coumarin derivatives yielded different dimers in water: parent coumarin **1a** yielded both syn head−head (60%) and syn head−tail (40%) dimers; 6-methyl coumarin **1b** gave syn head−head (15%) and anti head−head (85%) dimers; 7-methoxy coumarin **1c** yielded exclusively a syn head−tail dimer, while 8-methoxy coumarin **1d** was not soluble enough to perform photodimerization. Our goal was to orient all four coumarin derivatives, which produce different dimers in solution, to yield predominantly a single dimer within the Pd nanocage (Figure 1). This study was prompted by our recent

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[1] *Photochemistry in Constrained and Organized Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991.

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[3] (a) Hammond, G. S.; Stout, C. A.; Lamola, A. A. *J. Am. Chem. Soc.* **1964**, *86*, 3103−3106. (b) Hoffmann, R.; Wells, P.; Morrison, H. *J. Org. Chem.* **1971**, *36*, 102−108. (c) Morrison, H.; Curtis, H.; McDowell, T. *J. Am. Chem. Soc.* **1966**, *88*, 5415−5419. (d) Mustafa, A.; Kamel, M.; Allam, M. A. *J. Org. Chem.* **1957**, *22*, 888−891. (e) Wolff, T.; Gorner, H. *Phys. Chem. Chem. Phys.* **2004**, *6*, 368−376. (f) Yu, X.; Scheller, D.; Rademacher, O.; Wolff, T. *J. Org. Chem.* **2003**, *68*, 7386-7399.

[4] (a) Muthuramu, K.; Ramamurthy, V. *J. Org. Chem.* **1982**, *47*, 3976−3979. (b) Syamala, M. S.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 3712−3715. (c) Devanathan, S.; Ramamurthy, V. *J. Photochem. Photobiol., A* **1987**, *40*, 67−77.

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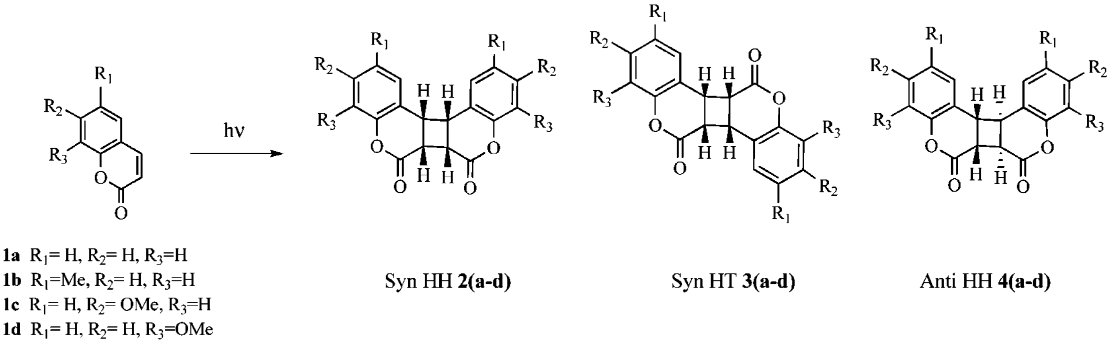
SCHEME 1. Photodimerization of Coumarin Derivatives (1a−1d) within the Pd Nanocage and in Aqueous Medium[a]



		Syn HH **2(a-d)**	Syn HT **3(a-d)**	Anti HH **4(a-d)**
1a	Water	60 (**2a**)	40 (**3a**)	-
	Pd-nanocage	>90 (**2a**)	-	-
1b	Water	15 (**2b**)	-	85 (**4b**)
	Pd-nanocage	>85 (**2b**)	-	-
1c	Water	-	>90 (**3c**)	-
	Pd-nanocage	>90 (**2c**)	-	-
1d	Water[a]	-	-	-
	Pd-nanocage	>90 (**2d**)	-	-

[a] Reported relative yields are based on conversion of the reactant. The conversion in all cases was less than 20%. Exact conversions are provided below in note (d). Higher conversion could not be achieved because of photoreversibility of the dimer. The following is detailed information regarding Scheme 1: (a) Dimer distribution in water could not be determined because of low solubility of **1d** in water. (b) The % of dimer formed was determined by integration of ^{1}H NMR signals. (c) Concentration of the Pd nanocage used: 6.68 × 10^{-3} M. Concentration of the guest used (**1a**−**1d**): 13.6 × 10^{-3} M. Concentration of the guests (**1a**−**1c**) for aqueous irradiation: ∼2 × 10^{-3} M. (d) For irradiations conducted within the Pd nanocage, the conversions to photoproduct after 10 h of irradiation were around 8% for **1a**, **1c**, **1d**, and 20% for **1b**. (e) For irradiations conducted in water, conversions to photoproduct were around 10% for **1a**, **1b**, and 30% for **1c** after 10 h (for **1a**, **1c**) and 1 h (for **1b**) of irradiation. (f) The selectivities in the photoproducts mentioned here are at the above conversions.

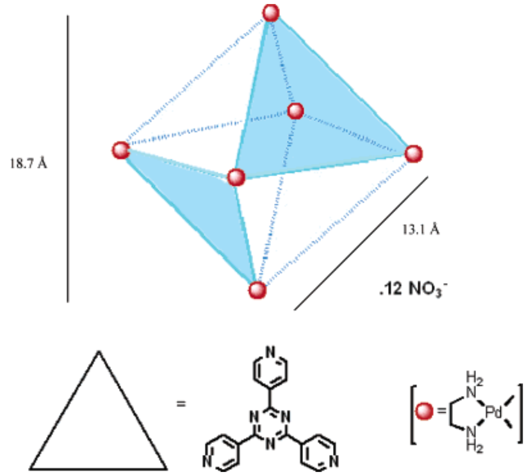


FIGURE 1. Structure of the Pd nanocage.

success with cucurbiturils as templates in orienting cinnamic acids and stilbazoles for photodimerization in water.[5] We succeeded in the above goal, and the results are summarized in the following section. Since we succeeded in reorienting the four systems, which yield different dimers to the same isomer, we did not feel it was necessary to explore numerous examples. In our view, the four examples have brought out the power of the host.

Results

Despite the ability of the Pd nanocage to include a variety of organic molecules, a serious limitation of the cage lies in its electronic absorption that extends up to 330 nm. Unless the cage can sensitize the reaction of the included guest molecules, its use is limited to guests absorbing at wavelengths longer than that of the cage. The absorption spectra of the cage and the three water-soluble coumarin derivatives are shown in Figure 2. The absorption characteristics of these three guest molecules are clearly conducive to direct excitation of the cage-included coumarins. The non water-soluble fourth coumarin used in this study is expected to have similar absorption spectrum.

The host−guest complexes (stoichiometry 1:2) of the Pd nanocage and coumarins **1a**−**1d**, respectively, were prepared by stirring required amounts of the host (6.7 × 10^{-3} M) and the guests (13.6 × 10^{-3} M) in 1 mL of D_2O. Details of the complexation procedure are described in the Experimental Section. The complexation between the Pd nanocage and the guest molecules **1a**−**1d** was confirmed by their ^{1}H NMR spectra. The upfield shift of protons of the guest from ^{1}H NMR analysis suggested host−guest complex formation. Although we

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[5] (a) Pattabiraman, M.; Arunkumar, N.; Kaanumalle, L. K. S.; Ramamurthy, V. *Org. Lett.* **2005**, *7*, 529−532. (b) Pattabiraman, M.; Arunkumar, N.; Raja, K.; Mague, J. T.; Ramamurthy, V. *Chem. Commun.* **2005**, *36*, 4542−4544.

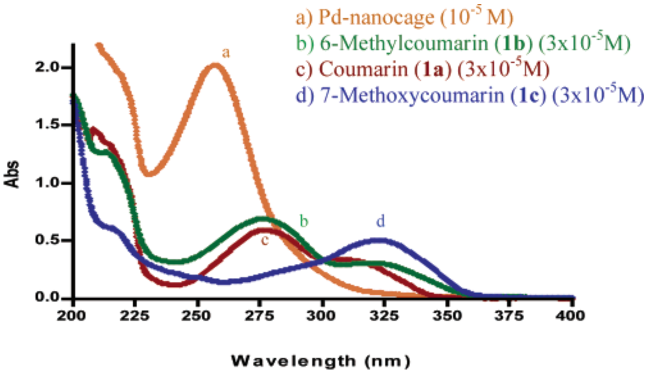
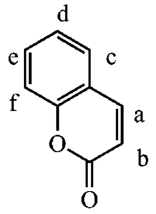
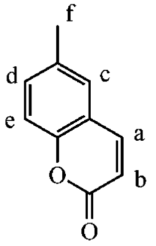
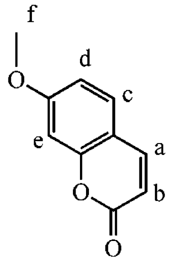
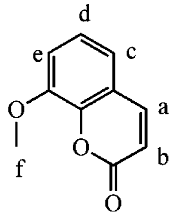


FIGURE 2. Absorption spectra of **1a**−**1c** and the Pd nanocage in water.

have used a 1:2 ratio of the host to the guest, the exact stoichiometry of the complex was unknown at this stage. Integration of the host and the guest proton signals suggested that the complex had a host−guest stoichiometry of 1:2, but as discussed below, there appeared to be an exchange between the free and the complexed guest molecules in the NMR time scale. Because of this phenomenon, the signals due to free and complexed guest molecules had the same chemical shifts. Two representative spectra for the complexes are provided in the Supporting Information (Figures S1 and S2). Aromatic, olefinic, as well as methoxy proton signals of 7-methoxy coumarin and 8-methoxy coumarin were shifted upfield (δ 1.5−2.5 ppm; Table 1) possibly because of an anisotropic ring current effect of the aromatic panels of the cage. Additional information regarding the nature of the host−guest complex was obtained by performing a titration of the host with coumarin **1a**. In this experiment, the changes in the chemical shifts of aromatic and olefinic protons of coumarin as a function of the added host were monitored by ^{1}H NMR. Continued upfield shifts in ^{1}H NMR signals of coumarin **1a** were observed when the host concentration increased (Figure 3). The absence of two independent signals from uncomplexed and complexed guest molecules suggested a fast exchange between these guest molecules in the NMR time scale. As seen in Figure 3, a continuous shift in the ^{1}H NMR signals was observed with a host−guest ratio of up to 1:3.5. Further addition of the host resulted in a very small shift that suggested most of the guest molecules are complexed to the Pd nanocage at a ratio of 1:3.5. To ensure that there is no reaction from the uncomplexed guest molecules, excess host was used during photochemical studies. As presented below, irradiations were conducted at various host−guest ratios, and the relative yield of the syn head−head dimer did not change when the host concentration was increased beyond 0.5 equivalents of the guest concentration, which suggested that at this concentration, the dimerization occurred mainly from the complexed coumarins.

The host−guest complexes of the Pd nanocage and coumarins **1a**−**1d** dissolved in water were irradiated with a 450 W medium-pressure Hg lamp for 10 h in Pyrex test tubes. Then, the samples were extracted with $CDCl_3$ and analyzed by ^{1}H NMR. The results obtained from photodimerization of coumarins **1a**−**1d** in water and within the host are provided in Scheme 1. The dimer conversion in all examples remained in the range of 10−20% even after 10 h of irradiation. The yields of the product reported in Scheme 1 were based on conversion of the reactant. We could not convert all the monomers to dimers in any case, and the maximum dimer obtained was only 20%. Such low conversion is common even during solution irradiation of coumarins.[3,4] It was reported earlier that the coumarin dimer reverts to the monomer under irradiated conditions.[4] We believe that this was likely to be the reason for our inability to achieve high conversion in the presence of the host. When irradiated as host−guest complexes, coumarins **1a**−**1d** gave the syn head−head dimers **2a**−**2d** as the main products. From comparisons of reported ^{1}H NMR signals due to cyclobutane and the aromatic proton, the main dimer with all four examples was identified to be the syn head−head isomer.[3] The NMR data for the syn head−head dimer of **1a** and **1b** are available in the literature.[3] The dimers from 7-methoxy coumarin and 8-methoxy coumarin had signals due to cyclobutane and aromatic protons in the region expected for syn head−head dimers. The importance of the host in altering the regiochemistry of the dimer was evident from irradiations conducted with different amounts of the Pd nanocage. ^{1}H NMR spectra of the cyclobutane region for irradiated samples with different amounts of the cage with coumarin **1a** and **1b** are provided in the Supporting Information (Figures S3 and S4).

TABLE 1. Changes in ^{1}H NMR Chemical Shift upon Complexation of Coumarins with Pd Nanocage

Compound		Change in chemical shift (ppm)[a] $\Delta = \delta_{\text{water}} - \delta_{\text{Pd-nanocage}}$
	**1a**	H_a - 1.1 H_b - 1.4 H_c - H_f - 1.7
	**1b**	H_a - 1.8 H_b - 1.5 H_c - H_e - 2.2 H_f - 1.3
	**1c**	H_a - 1.55 H_b - 2.05 H_d, H_e - 2.4 H_c - 1.45 H_f - 1.25
	**1d**	H_a - 1.5 H_b - H_e - 1.5 H_f - 1.7

[a] Concentration of the Pd nanocage: 6.68 × 10^{-3} M. Concentration of the guest (**1a**−**1d**): 13.6 × 10^{-3} M.

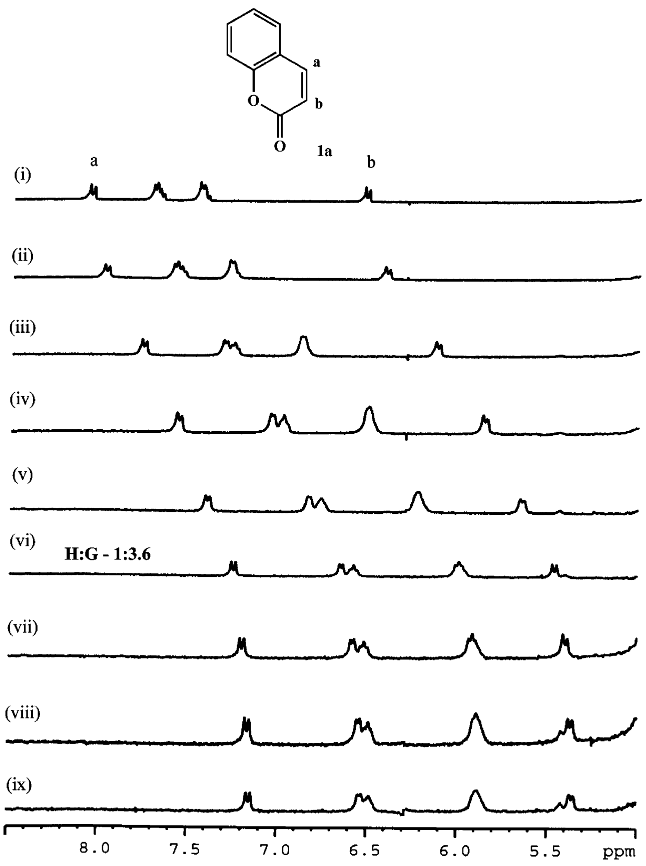


FIGURE 3. ^{1}H NMR (D_2O) spectra showing the changes in chemical shifts for the protons of **1a** (3.2 mM) upon addition of (i) 0, (ii) 0.02, (iii) 0.08, (iv) 0.14, (v) 0.20, (vi) 0.26, (vii) 0.32, (viii) 0.38, and (ix) 0.44 equiv of Pd nanocage.

Discussion

The octahedral Pd nanocage we used as the reaction medium was comprised of four triangular panels, which were connected to each other through a Pd^{2+} ion at each corner of the triangle. The alternate faces of the octahedron contained a tridendate ligand panel, while the other four faces of the octahedron were open (Figure 1). The four open faces of the octahedron were exposed to water. The distance between adjacent Pd^{2+} ions of the host was 13.1 Å and that of metal ions that were opposite to each other was 18.7 Å. By eliminating the narrow corners, we visualized the free space within the cage to be ∼10 × 15 Å. The nanocage included two molecules of *cis*-stilbene, *cis*-azobenzene, and benzil, and four molecules of adamantane.[6] Among the many clever applications[7] of the Pd nanocage designed by Fujita and co-workers, photodimerization of acenaphthylene and photocycloaddition of acenaphthylene to olefins were relevant to the current study.[8] They showed that the acenaphthylene within the cage yielded the syn dimer of acenaphthylene exclusively. While these results have opened up new opportunities, we felt that this particular example did not bring out the full potential of the Pd nanocage. Enhancement of the syn dimer formation from acenaphthylene within the nanocage was not very surprising when even direct excitation of it in solution resulted predominantly in the syn dimer.[9] It was in this context that we decided to examine the photodimerization of the nanocage-encapsulated coumarin derivatives **1a**−**1d** that yield different dimers in solution.

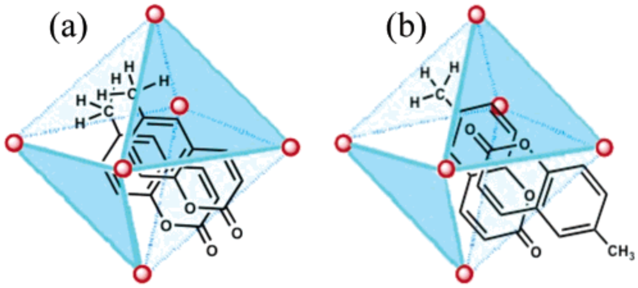


FIGURE 4. Possible orientations of **1b** within the host. Orientation of **1b** as shown in (a) will lead to syn head−head dimer and in (b) will lead to syn head−tail dimer.

At this stage, we do not have X-ray structural data of the host−guest complexes to support our intuitive model. On the basis of the assumption that the cage can accommodate two molecules of coumarins, the model we visualize to account for the selective dimerization is shown in Figure 4a,b. Inclusion of two coumarin molecules within the cage seems feasible based on reports of Fujita et al. demonstrating the encapsulation of two or three large molecules. We postulate that within the cage a pair of coumarin molecules would prefer to orient themselves in such a way that the polar carbonyl groups would face the aqueous exterior and the nonpolar aromatic groups would face within the hydrophobic interior (Figure 4a). Although the opposite faces of the octahedron cage have the same features, if the polar carbonyls face water through the open face, the aromatic parts of coumarin molecules, to protect themselves from water, would align at an angle to face the octahedron panel. The observed upfield ^{1}H NMR shifts of the aromatic and olefinic protons of coumarin are consistent with the idea that they are facing the aromatic panels of the host. We believe that such an arrangement would be stabilized by (coumarin) C−H−π (host panel) interactions and π−π interactions between the aromatic rings of the coumarin molecules. As seen in Figure 4a, this arrangement ideally is suited to yield syn head−head dimers. The alternate head−tail arrangement (Figure 4b), in which two coumarin molecules face water through opposite open faces, would result in a syn head−tail dimer. In this arrangement, one of the carbonyls would be within the cage and the methyl would be exposed to water. Hydrophobic forces would not favor such an arrangement. Furthermore, the weak interactions mentioned above that stabilize the head−head arrangement are not expected in this arrangement.

Another feature that could be responsible for selective formation of the syn head−head dimer is that of the four different dimers the syn head−head dimer is compact and would fit snugly within the cage.[10] The two anti dimers and syn head−tail dimer are too long in dimension and, therefore, would not fit completely within the cage and the aromatic parts would be

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[6] (a) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **2002**, *124*, 13576−13582.; (b) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **1999**, *121*, 1397−1398.

[7] Fujita, M.; Tominaga, M.; Hori, A.; Therrien, B. *Acc. Chem. Res.* **2005**, *38*, 371−380.

[8] (a) Yoshizawa, M.; Takeyama, Y.; Okano, T.; Fujita, M. *J. Am. Chem. Soc.* **2003**, *125*, 3243−3247. (b) Yoshizawa, M.; Takeyama, Y.; Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1347−1349. (c) Takaoka, K.; Kawano, M.; Ozeki, T.; Fujita, M. *Chem. Commun.* **2006**, *15*, 1625−1627.

[9] Cowan, D. O.; Drisko, R. L. E. *J. Am. Chem. Soc.* **1970**, *92*, 6286−6291.

exposed necessarily to the aqueous exterior. As discussed above, the precursor pairs of these dimers also would not fit completely within the nanocage. Thus, of the four arrangements yielding four different dimers, we believe a combination of hydrophobic, $\pi-\pi$, and C−H−π interactions between the host and the guest and the size and structure of the dimers favor the formation of the syn head−head dimer within the nanocage. An early attempt to control the regiochemistry of photocycloaddition was made by de Mayo et al. through the use of micelles.[11] This elegant approach relied on the concept that olefins with polar groups could be aligned at the interface between a hydrophobic interior and a hydrophilic exterior of a micelle. Although the authors did not succeed in obtaining complete control of the photodimerization of enones, they nevertheless illustrated the use of a hydrophobic−hydrophilic interface to align reactive molecules. As illustrated in this study, the same technique works much better when the reaction medium is much smaller in size and is able to interact with the reactant guest molecules through weak forces. We are exploring this concept with more examples and other confined nano spaces.

Summary

In this report, we established that the commercially available Pd nanocage was an ideal host to control the regiochemistry during the dimerization of olefins with a polar head group. Although we were unable in the past to orient the same coumarins at the hydrophobic and hydrophilic boundaries of a micelle, we accomplished it within the much smaller nano reaction vessel having similar boundaries in water. The small and better-defined features of the Pd nanocage enabled us to achieve better control of product distributions. We continue to explore the use of the Pd nanocage as a reaction medium for photochemical reactions.

Experimental Section

Chemicals. The host (Pd nanocage), coumarins (**1a,b,c**), 2,3-dihydroxybenzaldehyde, carbethoxymethylene triphenylphosphorane, and N,N-diethylaniline procured from commercial sources were used as such. Coumarin **1d** was synthesized following the literature procedure.[12]

Complexation of 1a−1d with Pd Nanocage. Required amounts of the guest (G) **1a**−**1d** (**1a**, 2 mg (13.6×10^{-3} M), **1b**, 2.2 mg (13.7×10^{-3} M), and **1c** or **d**, 2.4 mg (13.6×10^{-3} M)) were stirred with 7 mg (2.33×10^{-3} M) or 20 mg (6.68×10^{-3} M) of the host (H) in 1 mL of D_2O in a hot water bath for 5 h to obtain a clear solution of the inclusion complex with a H−G ratio of 1:6 or 1:2. The solution then was filtered to remove any undissolved particles using Whatman filter paper of fine porosity. ^{1}H NMR spectra were recorded to confirm the complexation. The solution then was irradiated for 10 h using a 450 W medium-pressure Hg lamp. The products then were extracted by stirring (3 h) with $CDCl_3$, dried over anhydrous sodium sulfate, and analyzed by ^{1}H NMR. The conversion to product was determined by NMR integration of peaks of the starting material (**1a**−**1d**) and that of the dimer formed. The percentages of dimers formed were determined based on the integration of the NMR signals of either cyclobutane or aromatic protons. The conversion was around 8% for coumarins **1a**,**c**, and **d,** whereas the conversion was around 20% for coumarin **1b** when the reaction was conducted within the Pd nanocage. The amount of syn head−head dimers (**2a**−**2d**), which were obtained upon irradiation of **1a**−**1d** within the Pd nanocage, was around 0.14 mg (**2a**, 7% yield), 0.43 mg (**2b**, 18% yield), 0.18 mg (**2c**, 7% yield), and 0.13 mg (**2d**, 5% yield).

NMR Titration Studies. A known amount of **1a** (2−3 mg) was stirred with 1 mL of D_2O for 12 h. The solution then was filtered with Whatman filter paper of fine porosity, and the ^{1}H NMR was recorded. The host (0.3 mg) was added sequentially to this solution, sonicated for 10−15 min, and then ^{1}H NMR spectra were recorded until the amount of added host was 4.2 mg. The H−G ratio was determined by integration of the peaks corresponding to the host and the guest.

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Supporting Information Available: ^{1}H NMR spectra of the host−guest complexes of **1c**,**d**, ^{1}H NMR spectra showing the cyclobutane region of the dimers obtained upon irradiation of **1a**,**b** in water and as a host−guest complex, and the ^{1}H NMR characterization of the dimers obtained. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Molecular dimensions of the dimers of 6-methyl coumarin estimated through Chem 3D Ultra are (a) syn head−head (width, 9.1 Å, height, 8.1 Å); (b) syn head−tail (width, 8.2 Å, height, 12.3 Å); (c) anti head−head (width, 11.5 Å, height, 9.1 Å); (d) anti head−tail (width, 6.5 Å, height, 13.5 Å).

[11] Berenjian, N.; de Mayo, P.; Sturgeon, M.-E.; Syndnes, L. K.; Weedon, A. C. *Can. J. Chem.* **1982**, *60*, 425−436.

[12] Cerqueira, F. S. A.; Oliveira-Campos, A. M. F.; Coelho, P. J.; Melo de Carvalho, L. H.; Samat, A.; Guglielmetti, A. R. *Hel. Chim. Acta.* **2002**, *85*, 442−450.